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ORIGINAL PAPER

Genetic Factors Affecting Late-Onset Alzheimer's Disease Susceptibility

Maryam Rezazadeh[1] · Aziz Khorrami[1] · Tarlan Yeghaneh[1] · Mahnaz Talebi[2] · Seyed Jalal Kiani[3] · Yaser Heshmati[4] · Jalal Gharesouran[1]

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Abstract Alzheimer's disease is considered a progressive brain disease in the older population. Late-onset Alzheimer's disease (LOAD) as a multifactorial dementia has a polygenic inheritance. Age, environment, and lifestyle along with a growing number of genetic factors have been reported as risk factors for LOAD. Our aim was to present results of LOAD association studies that have been done in northwestern Iran, and we also explored possible interactions with apolipoprotein E (APOE) status. We re-evaluated the association of these markers in dominant, recessive, and additive models. In all, 160 LOAD and 163 healthy control subjects of Azeri Turkish ethnicity were studied. The Chi-square test with Yates' correction and Fisher's exact test were used for statistical analysis. A Bonferroni-corrected p value, based on the number of statistical tests, was considered significant. Our results confirmed that chemokine receptor type 2 (*CCR2*), estrogen receptor 1 (*ESR1*), toll-like receptor 2 (*TLR2*), tumor necrosis factor alpha (*TNFα*), *APOE*, bridging integrator 1 (*BIN1*), and phosphatidylinositol-binding clathrin assembly protein (*PICALM*) are LOAD susceptibility loci in Azeri Turk ancestry populations. Among them, variants of *CCR2*, *ESR1*, *TNFα*, and *APOE* revealed associations in three different genetic models. After adjusting for *APOE*, the association (both allelic and genotypic) with *CCR2*, *BIN1*, and *ESRα* (*Pvu*II) was evident only among subjects without the *APO*E ε4, whereas the association with *CCR5*, without Bonferroni correction, was significant only among subjects carrying the *APOE* ε4 allele. This result is an evidence of a synergistic and antagonistic effect of APOE on variant associations with LOAD.

Keywords Alzheimer's disease · Association · Polymorphism · *APOE* · Neurodegenerative diseases · Azeri Turkish

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and represents a serious public health problem worldwide (Cacabelos et al. 2005; Defina et al. 2013). AD is categorized into two major groups, early-onset (EOAD) and late-onset Alzheimer's disease (LOAD), differing in terms of their symptomatic, biological, genetic, and neurophysiological characteristics (Biagioni and Galvin 2011). EOAD corresponds to <1–6 % of all cases of Alzheimer disease (Avramopoulos 2009). This condition is inherited in an autosomal dominant pattern and caused by highly penetrant mutations in one of the three known genes (PSEN1, PSEN2, and APP). Affected people with this type of disease have the disease onset prior to age 65 (Goate et al. 1991; Levy-Lahad and Bird 1996; Sherrington et al. 1996).

In contrast to EOAD, sporadic or late-onset Alzheimer's disease has heterogeneous etiology and affects individuals

✉ Jalal Gharesouran
Gharesouranj@tbzmed.ac.ir

[1] Department of Medical Genetics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Neuroscience Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[3] Virology Department, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Medicine, Huddinge, H7, Karolinska Institutet, Stockholm, Sweden

older than 65 years with modest or no familial clustering (Bird 2008; Cacabelos et al. 2005; Zetzsche et al. 2010).

Although LOAD patients exhibit no clear pattern of inheritance, twin and family-based studies have suggested a significant genetic component in the etiology of LOAD (Gatz et al. 2005, 2010). Results of scientific research have implicated complex interactions between different genetic variants, age, gender, and other environmental factors that modulate LOAD risk (Goldman et al. 2011; Reitz et al. 2011).

According to these studies, the estimated heritability in LOAD ranges from 25 to 75 % (Wilson et al. 2011). In addition to the ε4 allele of the apolipoprotein E gene (*ApoE*), which is the only genetic factor that unambiguously confers increased risk of LOAD, recent GWASs (genome-wide association studies) have implicated loci of other genes with more modest effects on this disease (Table 1).

Some of these loci are mapped to genes with established roles in Aβ metabolism [APOE, apolipoprotein J (clusterin), phosphatidylinositol-binding clathrin assembly protein], neuroinflammation (complement receptor 1, tumor necrosis factor-α, T cell receptor, CRR2, CRR5), calcium signaling (calcium homeostasis modulator 1), and hormonal regulation (estrogen receptor 1), and all are recognized as novel putative LOAD risk loci (www.alzgene.org).

APOE exerts its effect on the risk and age of onset distribution in a dose-related manner (Sando et al. 2008). APOE protein plays a critical role in Aβ (amyloid β) homeostasis, promotes the proteolytic clearance of amyloid β, and functions as a chaperone (Liu et al. 2009; Schellenberg and Montine 2012). Clusterin is a multifunctional glycoprotein. Both APOE and clusterin molecules are involved in Aβ metabolism and deposition and are protective agents against Aβ neurotoxicity (Koren et al. 2009). Both PICALM and BIN1 are ubiquitously expressed genes, most abundantly in the brain, and are involved in intracellular trafficking of proteins such as vesicle-associated membrane protein 2 (VAMP2) and neurotransmitters through clathrin-mediated endocytosis (CME) (Ando et al. 2013; Harel et al. 2008; Parikh et al. 2014; Xiao et al. 2012).

Neuroinflammation as a common feature of the brain pathology presents in Alzheimer's disease is associated with immune mediators's up-regulation. TNFα, a pro-inflammatory cytokine, a well-known immune mediator with modulating effects on memory and synaptic function, is up-regulated in AD patients and animal models of the disease (McAlpine et al. 2009; Tweedie et al. 2012).

CCR2, CCR5, and their related ligands are involved in the accumulation of microglia at sites affected by neuroinflammation (Galimberti et al. 2004; Navratilova 2006). CCR2 and its ligand CCL2 (MCP-1) is involved in the metabolism of Aβ, and CCR5 receptor has role in the regulation of brain immune responses in AD (Harries et al. 2012). A valine to isoleucine substitution at codon 64 within the first membrane region of CCR2, CCR2V64I, causes a controversial influence on the expression of CCR2 on the cell surface, while CCR5Δ32 polymorphism creates a premature stop codon and has a protective effect toward inflammatory diseases such as AD (Sezgin et al. 2011).

Toll-like receptor 2 (TLR2), located in the Alzheimer dementia (AD) linkage region on 4q, is involved in the microglia-mediated inflammatory response (Blacker et al. 2003; Landreth and Reed-Geaghan 2009). TLR2 is a member of pattern recognition receptors in the innate immune system. TLR2 may also be essential for Aβ clearance and in that way provides neuroprotection in AD (Bsibsi et al. 2002; Richard et al. 2008). Calcium homeostasis modulator 1 (CALHM1), mainly expressed in the hippocampus, encodes a multipass transmembrane glycoprotein that controls cytosolic Ca^{2+} concentrations and Aβ levels (Shoji et al. 2005). A non-synonymous polymorphism, rs2986017 (p.P86L) in the CALHM1 gene, was reported to affect calcium homeostasis and promotes Aβ accumulation via a loss of CALHM1 control on Ca^{2+} permeability and cytosolic Ca^{2+} levels and increases the risk of AD (Dreses-Werringloer et al. 2008).

ESR1 is one of the receptors through which estrogen exerts its biological effects and mediates the effects of estrogen on AD (Sundermann et al. 2010). According to some reports, AD is more prevalent in women, and the use of estrogen by women after menopause is associated with a lower risk of AD or delayed disease (Ma et al. 2009). Numerous laboratory studies have demonstrated inhibitory effects of estrogen on Aβ plaque formation and its antioxidant and anti-apoptotic functions (Ba et al. 2004; Chiueh et al. 2003).

We aimed to examine the possible associations of 19 different risk factors for LOAD, identified recently by GWAS, in different genetic models, and their possible interaction with *ApoE* genotype conditions in LOAD within the Azeri Turkish population of Iran.

Materials and Methods

A total of 160 patients, 66 males and 94 females (age range between 65 and 99 and mean age 76.06 ± 7.75 years), with LOAD were recruited from northwest of Iran. The patients were screened by their physicians in the Neuroscience Research Center between February 2010 and July 2014 according to the DSM-IV diagnostic criteria (American Psychiatric Association 1994; Alberoni et al. 2000) and were referred to our laboratory for genotyping of

Table 1 Investigated SNPs, previously explored in different genome-wide association studies, case–control studies, and family-based studies

Gene	Marker	Ref SNP alleles	Minor allele	Case–control studies	GWAS studies	Family-based studies (by ethnic group)
CCR2	rs1799864	A/G	A	AlzGene, Nishimura et al. (2003), Galimberti et al. (2004), Huerta et al. (2004), Giedraitis et al. (2009)	–	–
CCR5	rs333	–	–	AlzGene, Combarros et al. (2004), Galimberti et al. (2004), Huerta et al. (2004), Balistreri et al. (2006)	–	–
CALHM1	rs2986017	A/G	A	AlzGene, Bertram et al. (2008), Dreses-Werringloer et al. (2008), Cui et al. (2009), Inoue et al. (2010), Minster et al. (2009), Tan et al. (2011), Boada et al. (2010), Shibata et al. (2010)	Ripke et al. (2013)	Bertram et al. (2008)
TNFα	rs1800629	A/G	A	AlzGene, Tarkowski et al. Alvarez et al. (2002), Culpan et al. (2003), Randall et al. (2009)	–	Collins et al. (2000)
	rs1800630	A/C	A			
PICALM	rs541458	C/T	C	AlzGene, Jones et al. (2010), Lambert et al. (2011), Lee et al. (2011), Naj et al. (2011), Masoodi et al. (2013)	Seshadri et al. (2010), Hu et al. (2011)	Wijsman et al. (2011)
	rs17159904	A/G	G			
	rs12800974	C/G/T	C/G			
CR1	rs3818361	C/T(REV)	A	AlzGene, Harold et al. (2009), Lambert et al. (2009), Corneveaux et al. (2010), Jones et al. (2010), Jun et al. (2010), Kamboh et al. (2012), Zhang et al. (2010), Naj et al. (2011), Wijsman et al. (2011), Shi et al. (2012)	Harold et al. (2009), Naj et al. (2011), Hollingworth et al. (2011), Hu et al. (2011)	Wijsman et al. (2011)
	rs6701713	A/G	A			
	rs1408077	G/T (REV)	A			
BIN1	rs744373	C/T	G	AlzGene,Harold et al. (2009), Jones et al. (2010), Seshadri et al. (2010), Hu et al. (2011), Lambert et al. (2011), Lee et al. (2011),Naj et al. (2011), Wijsman et al. (2011), Kamboh et al. (2012), Shi et al. (2012), Masoodi et al. (2013)	Harold et al. (2009), Naj et al. (2011), Hollingworth et al. (2011), Hu et al. (2011), Lee et al. (2011), Beecham et al. (2014)	Wijsman et al. (2011)
	rs11554585	A/G	G			
	rs7561528	A/G	A			
APOE	rs2075650	A/G	G	AlzGene,Harold et al. (2009), Shi et al. (2012), Jones et al. (2010), Seshadri et al. (2010), Hostage et al. (2013)	Coon et al. (2007), Li et al. (2008), Abraham et al. (2008), Beecham et al. (2009), Carrasquillo et al. (2010), Lambert et al. (2009), Seshadri et al. (2010)	Corder et al. (1994), Houlden et al. (1994), Farrer et al. (1995), Blacker et al. (1997), Bertram et al. (2008), Wijsman et al. (2011)

Table 1 continued

Gene	Marker	Ref SNP alleles	Minor allele	Case–control studies	GWAS studies	Family-based studies (by ethnic group)
CLU	rs11136000	C/T	T	AlzGene,Harold et al. (2009), Lambert et al. (2009), Biffi et al. (2010), Carrasquillo et al. (2010), Corneveaux et al. (2010), Jun et al. (2010), Naj et al. (2011), Seshadri et al. (2010), Yu et al. (2010), Hu et al. (2011), Kamboh et al. (2012), Lee et al. (2011)	Naj et al. (2011)	Wijsman et al. (2011)
TLR2	−196 to −174 del	–	–	Yu et al. (2011), Wang et al. (2011)	–	–
ESRα	rs2234693	C/T	C	AlzGene, Brandi et al. (1999), Ji et al. (2000), Mattila et al. (2000), Lambert et al. (2001), Lin et al. (2003), Blomqvist et al. (2006), Corbo et al. (2006), Porrello et al. (2006), Combarros et al. (2007), Ma et al. (2009)	–	–
	rs9340799	A/G	G			

SNP single nucleotide polymorphism, GWAS genome-wide association studies

candidate genes. The control group consisted of 163 ethnically, sex-matched 68 male and 95 female (age range between 65 and 89 and mean age 75.29 ± 6.75 years) participants. They underwent neurological and medical examinations, which showed that they were free of any symptoms suggestive of cognitive decline (Gharesouran et al. 2014). Among different racial or ethnic groups living in Iran, including Persian (51 %), Azeri Turk (24 %), Kurd (7 %), Arab (3 %), and other minorities, we limited our investigation to 15–24 million Azeri Turks in northwestern Iran.

Excluding patients with disease onset age before 65 years and from families with two or more affected people within more than one generation, ensured the sporadic form of the disease (Ray et al. 1998). Written informed consent was obtained from each participant, or their legally authorized representatives, who were accepted previously by the ethics committee of special clinics at the Tabriz University of Medical Sciences. This study was approved by the review board of the Neuroscience Research Center and Immunology Research Center at the Tabriz University of Medical Sciences.

Variants on *CR1*, *PICALM*, *BIN1*, and *APOE* genes were genotyped by PCR and direct sequencing. Genotypes related to polymorphisms on *TNFα*, *CCR2*, *CLU*, *TLR1*, and *ESRα* genes were determined by PCR–RFLP reaction, and the *CCR5*Δ32 genotype was determined by PCR without RFLP. The purified PCR products of these genes from AD cases and healthy controls were randomly sequenced bidirectionally (Gharesouran et al. 2014).

The Hardy–Weinberg equilibrium (HWE) was estimated using the Chi-square test. Differences in allele and genotype distribution between the LOAD patients and healthy controls were analyzed using the Chi-square and Fisher's exact tests. We used the Bonferroni method to adjust for multiple statistical tests. A Bonferroni-corrected p value of 0.05 (based on the number of SNPs analyzed and genetic models) was regarded as statistically significant. The odds ratio (OR) was calculated at 95 % confidence interval (CI), whenever possible.

To assess the role of interaction of the APOE ε4 allele with these polymorphisms, the stratified analysis was performed regarding the existing of ApoE ε4 allele. To adjust case and control for APOE ε4 status, subjects were divided into the APOE ε4-positive and APOE ε4-negative subgroups. In addition, the significance of the SNPs association with LOAD was tested in the dominant, additive, and recessive models for SNPs with minor allele homozygote counts of more than 14.

Results

Allele and genotype distribution of the investigated SNPs is shown in Table 2. The distributions of investigated markers were in HWE for both AD patients and controls ($p > 0.05$, corrected $p = 0.003$). Allele distributions in *CCR2* (rs1799864), *TNFα* (rs1800629), *PICALM* (rs541458), *BIN1* (rs744373), *APOE*, *TLR2* (−196 to −174 Del), *ESRα* (*Pvu*II), and *ESRα* (*Xba*I) (8 of the 19 investigated polymorphisms) were significantly different between the LOAD and control groups. However, CALHM1 (rs2986017) showed nominally significant association with an increased risk of LOAD, but missed criteria for significance after Bonferroni correction ($p = 0.01$, corrected $p = 0.19$).

Significant differences were revealed in genotype distribution of *CCR2* (rs1799864), *CALHM1* (rs2986017), *TNFα* (rs1800629), *PICALM* (rs541458), *APOE*, *CLU* (rs11136000), and *TLR2* (−196 to −174del) polymorphisms among the LOAD and control groups in this ethnic group (Table 2). *CALHM1* (rs2986017), *CLU*

Table 2 Genotype frequencies, allele frequencies, and statistical analysis results for 19 investigated polymorphisms of different genes among LOAD patients and control subjects

SNPs	Genotype no. (%)							Allele no. (%)					OR; 95 % CI
	mm		mM		MM		*p*	m		M		*p*	
	AD	Con	AD	Con	AD	Con		AD	Con	AD	Con		
rs1799864	2 (1.3)	21 (12.9)	25 (15.6)	59 (36.2)	133 (83.1)	83 (50.9)	<0.0001	29 (9.1)	101 (31.0)	291 (90.9)	225 (69.0)	<0.0001	0.222 (0.142–0.347)
rs333	0 (0.0)	0 (0.0)	20 (12.5)	14 (8.6)	140 (87.5)	149 (91.4)	0.33	20 (6.3)	14 (4.3)	300 (93.8)	312 (95.7)	0.348	1.486 (0.737–2.995)
rs2986017	2 (1.3)	1 (0.6)	31 (19.4)	15 (9.2)	127 (79.4)	147 (90.2)	0.025	35 (10.9)	17 (5.2)	285 (89.1)	309 (94.8)	0.011	2.232 (1.223–4.073)
rs1800629	35 (21.9)	0 (0.0)	73 (45.6)	20 (12.3)	52 (32.5)	143 (87.7)	<0.0001	143 (44.7)	20 (6.1)	177 (55.3)	306 (93.9)	<0.0001	12.361 (7.473–20.445)
rs1800630	1 (0.6)	1 (0.6)	19 (11.9)	13 (8.0)	140 (87.5)	149 (91.4)	0.502	21 (6.6)	15 (4.6)	299 (93.4)	311 (95.4)	0.3593	1.456 (0.737–2.878)
rs541458	11 (6.9)	1 (0.6)	40 (25.0)	22 (13.5)	109 (68.1)	140 (85.9)	0.0002	62 (19.4)	24 (7.4)	258 (80.6)	302 (92.6)	<0.0001	3.023 (1.834–4.983)
rs12800974	2 (1.3)	0 (0.0)	11 (6.9)	8 (4.9)	147 (91.9)	155 (95.1)	0.2647	15 (4.7)	8 (2.5)	305 (95.3)	318 (97.5)	0.187	1.954 (0.817–4.677)
rs17159904	2 (1.3)	1 (0.6)	6 (3.8)	5 (3.1)	152 (95.0)	157 (96.3)	0.78	10 (3.1)	7 (2.1)	310 (96.9)	319 (97.9)	0.596	1.47 (0.552–3.91)
rs6701713	1 (0.6)	0 (0.0)	14 (8.8)	9 (5.5)	145 (90.6)	154 (94.5)	0.31	16 (5.0)	9 (2.8)	258 (80.6)	302 (92.6)	0.203	0.539 (0.235–1.239)
rs3818361	1 (0.6)	0 (0.0)	7 (4.4)	5 (3.1)	152 (95.0)	158 (96.9)	0.49	9 (2.8)	5 (1.5)	311 (97.2)	321 (98.5)	0.396	1.857 (0.615–5.605)
rs1408077	2 (1.3)	0 (0.0)	5 (3.1)	5 (3.1)	153 (95.60)	158 (96.9)	0.358	10 (3.1)	4 (1.2)	310 (96.9)	322 (98.8)	0.3961	1.857 (0.615–5.605)
rs744373	11 (6.9)	1 (0.6)	19 (11.9)	14 (8.6)	130 (81.3)	148 (90.8)	0.006	41 (12.8)	16 (4.9)	279 (87.2)	310 (95.1)	<0.0001	2.847 (1.562–5.187)
rs11554585	1 (0.6)	1 (0.6)	16 (10.0)	12 (7.4)	143 (89.4)	150 (92.0)	0.7	18 (5.6)	14 (4.3)	302 (94.4)	312 (95.7)	0.5485	1.328 (0.649–2.718)
rs7561528	1 (0.6)	0 (0.0)	20 (12.5)	13 (8.0)	139 (86.9)	150 (92.0)	0.23	22 (6.9)	13 (4.0)	298 (93.1)	313 (96.0)	0.1482	1.77 (0.879–3.592)
rs2075650	29 (18.1)	2 (1.2)	38 (23.8)	14 (8.6)	93 (58.1)	147 (90.2)	<0.001	96 (30.0)	18 (5.5)	224 (70.0)	308 (94.5)	<0.0001	7.333 (4.307–12.484)
rs11136000	42 (26.3)	26 (16.0)	93 (58.1)	121 (74.2)	25 (15.6)	16 (9.8)	0.009	177 (55.3)	173 (53.1)	143 (44.7)	153 (46.9)	0.624	1.095 (0.803–1.492)
−196 to −174 del	30 (18.8)	18 (11.0)	91 (56.9)	72 (44.2)	39 (24.4)	73 (44.8)	0.0004	151 (47.2)	108 (33.1)	169 (52.8)	218 (66.9)	0.00036	1.803 (1.312–2.479)
rs2234693	36 (22.5)	16 (9.8)	94 (58.8)	69 (42.3)	30 (18.8)	78 (47.9)	0.025	166 (51.9)	101 (31.0)	154 (48.1)	225 (69.0)	<0.0001	0.484 (0.351–0.667)
rs9340799	27 (16.9)	11 (6.7)	41 (25.6)	36 (22.1)	92 (57.5)	116 (71.2)	0.007	95 (29.7)	58 (17.8)	225 (70.3)	268 (82.2)	0.00053	1.951 (1.345–2.829)

AD the number of LOAD patients, *Con* controls, *M* major allele, *m* minor allele, *CI* confidence interval, *OR* odds ratio. Correction for multiple testing was carried out using the Bonferroni adjustment. The significance of the *p* value was assessed at 0.003 (0.05/19 considering 19 SNPs tested)

(rs11136000), *BIN1* (rs744373), *ESRα* (PvuII), and *ESRα* (XbaI) genotype distributions among the LOAD and control groups were only significant before Bonferroni correction (Table 2).

As shown in Table 3, seven markers, *CCR2* (rs1799864), *CLU* (rs11136000), *ESRα* (PvuII), *ESRα* (XbaI), *TLR2* (−196 to −174 del), *TNFα* (rs1800629), and *APOE* had minor allele homozygote counts more than 14, and the significance of their associations with LOAD was tested in a dominant, additive, and recessive model.

Among them, *CCR2* (rs1799864), *ESRα* (PvuII), *ESRα* (XbaI), *TNFα* (rs1800629), and *APOE* were correlated with the LOAD in three different statistical models. However, ESRα (PvuII) in dominant model and ESRα (XbaI) in dominant and recessive models missed their correlations with the LOAD after Bonferroni correction (corrected significant $p = 0.002$).

TLR2 (−196 to −174 del) was associated with the risk of LOAD only in the additive and dominant models (recessive model $p = 0.073$), and *CLU* (rs11136000) showed no association with LOAD in additive and dominant models ($p = 0.27$ and $p = 0.16$, respectively). *CLU* (rs11136000) association with LOAD in recessive model ($p = 0.0329$) missed after Bonferroni correction (Table 3).

After adjusting for *APOE*, statistical analysis of the allelic distribution showed an association with *PICALM* (rs541458), *BIN1* (rs744373), *CCR2* (rs1799864), *TNFα* (rs1800629), *TLR2* (−196 to −174 del), and *ESRα* (PvuII) only among subjects without the *APOE* ε4 allele. The association with *CCR5, ESRα* (XbaI), and *TNFα* (rs1800630) was evident only among subjects with the *APOE* ε4 allele.

Among them *PICALM* (rs541458), CCR5 (rs333), *and ESRα* (XbaI) missed their association after Bonferroni correction (corrected significant $p = 0.003$).

The interactions of other SNPs with the *APOE* ε4 allele were not statistically significant. The genotype distribution of the investigated SNPs after adjusting for *APOE* is shown in Table 4.

Discussion

Alzheimer's disease is clinically characterized by a progressive decline of memory with pathogenic features including amyloid plaques, oxidative stress, dysfunctional calcium homeostasis, hormonal dysregulation, and decline in immune system function (Melesie and Dinsa 2013; Wuwongse et al. 2010). AD, particularly multifactorial type, LOAD, is immensely complex on the molecular level (Bertram and Tanzi 2012).

In this article, we report the results of case–control investigations of potential risk factors for LOAD in northwestern Iran of patients with Azeri Turkish origin (Gharesouran et al. 2013). We also re-examined the SNPs association with LOAD in different genetic models. We then compared allele and genotype distribution of the variants after adjustment for APOE status. Overall in the present study, 19 of the most replicated markers association with LOAD were assessed (Table 2).

The ε4 allele of apolipoprotein E accounts for 20–70 % of the LOAD risk and offers odds ratios (ORs) ranging from 6 to 30 in the APOE ε4/ε4 genotype carriers for disease association (Ertekin-Taner 2007, 2010; Corneveaux et al. 2010). APOE ε4, compared with APOE ε3 and APOE ε2, has less three-dimensional folding stability (Koren et al., 2009; Mahley and Huang 2006; Hatters et al. 2006). APOE ε4 is also not as efficient at repairing neuronal damage, transporting cholesterol, and delivery of cholesterol to neurons as ApoE ε3 (Liu et al. 2009; Kok et al. 2011).

Table 3 Re-evaluation of the association of 7 markers with minor allele homozygote counts more than 14, in dominant, recessive, and additive models

Gene	Markers	Additive models		Dominant models		Recessive models	
		p	OR; 95 % CI	*p*	OR; 95 % CI	*p*	OR; 95 % CI
CCR2	rs1799864	<0.0001	0.179 (0.109–0.294)	<0.0001	0.210 (0.126–0.353)	<0.0001	0.086 (0.02–0.372)
CLU	rs11136000	0.27	0.655 (0.338–1.269)	0.161	0.588 (0.301–1.148)	0.0329	1.876 (1.085–3.243)
ESRα	rs2234693	<0.0001	4.273 (2.622–6.964)	<0.0001	3.976 (2.407–6.5695	0.0031	2.668 (1.413–5.036)
	rs9340799	0.00115	2.065 (1.349–3.162)	0.01438	1.824 (1.150–2.894)	0.008	2.805 (1.340–5.872)
TLR2	−196 to −174 del	<0.0001	2.617 (1.651–4.148)	0.00018	2.516 (1.565–4.046)	0.073189	1.859 (0.989–3.492)
TNFα	rs1800629	<0.0001	19.663 (11.171–34.609)	<0.0001	14.85 (8.372–26.339)	<0.0001	19.663 (11.171–34.609)
ApoE	rs2075650	<0.0001	8.430 (4.784–14.85)	<0.0001	6.619 (3.618–12.109)	<0.0001	17.821 (4.175–76.075)

AD the number of LOAD patients, *Con* controls, *CI* confidence interval, *OR* odds ratio. The significance of the *p* value (after Bonferroni adjustment) was assessed at 0.003 {0.05/(7SNPx 3 genetic models)}

Table 4 Allelic and genotypic distribution of investigated polymorphisms in cases and controls stratified by *APOE* ε4 allele status

SNPs	Genotype no. (%). *APOE* ε4 allele carriers							Allele no. (%) *APOE* ε4 allele carriers					OR; 95 % CI
	mm		Mm		MM		*p*	m		M		*p*	
	AD	Con	AD	Con	AD	Con		AD	Con	AD	Con		
rs1799864	1 (0.6)	1 (0.6)	22 (13.8)	2 (1.2)	25 (15.6)	6 (3.7)	0.18	24 (7.5)	4 (1.2)	72 (22.5)	14 (4.3)	1	–
rs333	0 (0.0)	0 (0.0)	18 (11.3)	8 (4.9)	30 (18.8)	1 (0.6)	0.007	18 (5.6)	8 (2.5)	78 (24.4)	10 (3.1)	0.03	–
rs2986017	1 (0.6)	0 (0.0)	22 (13.8)	3 (1.8)	25 (15.6)	6 (3.7)	0.686	24 (7.5)	3 (0.9)	72 (22.5)	15 (4.6)	0.55	–
rs1800629	26 (16.3)	0 (0.0)	19 (11.9)	4 (2.5)	3 (1.9)	5 (3.1)	0.0001	71 (22.2)	14 (4.3)	25 (7.8)	4 (1.2)	0.78	–
rs1800630	1 (0.6)	1 (0.6)	10 (6.3)	3 (1.8)	37 (23.1)	2 (1.2)	0.0416	12 (3.8)	8 (2.5)	84 (26.3)	10 (3.1)	<0.0001	18.2 (5.505 –60.167)
rs541458	7 (4.4)	1 (0.6)	24 (15.0)	6 (3.7)	17 (10.6)	3 (1.8)	0.90	38 (11.9)	8 (2.5)	58 (18.1)	12 (3.7)	0.841	0.963 (0.343–2.698)
rs12800974	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	47 (29.4)	9 (5.5)	0.66	1 (0.3)	0 (0.0)	95 (29.7)	18 (5.5)	1	–
rs17159904	1 (0.6)	0 (0.0)	3 (1.9)	1 (0.6)	44 (27.5)	8 (4.9)	0.7989	5 (1.6)	1 (0.3)	91 (28.4)	17 (5.2)	1	–
rs6701713	1 (0.6)	0 (0.0)	5 (3.1)	1 (0.6)	42 (26.3)	8 (4.9)	0.9082	7 (2.2)	1 (0.3)	89 (27.8)	17 (5.2)	1	–
rs3818361	1 (0.6)	0 (0.0)	2 (1.3)	0 (0.0)	45 (28.1)	9 (5.5)	0.7431	4 (1.3)	0 (0.0)	92 (28.8)	18 (4.6)	0.61	–
rs1408077	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	46 (28.8)	8 (4.9)	0.3704	3 (0.9)	1 (0.3)	93 (29.1)	17 (5.5)	1	1.824 (0.179–18.584)
rs744373	1 (0.6)	1 (0.6)	3 (1.9)	1 (0.6)	44 (27.5)	7 (4.3)	0.7578	5 (1.6)	3 (0.9)	91 (28.4)	15 (4.6)	0.11	–
rs11554585	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	48 (30.0)	9 (5.5)	1	0 (0.0)	0 (0.0)	96 (30.0)	18 (5.5)	1	–
rs7561528	0 (0.0)	0 (0.0)	4 (2.5)	2 (1.2)	44 (27.5)	7 (4.3)	0.237	4 (1.3)	2 (0.6)	92 (28.8)	16 (4.9)	0.239	2.875 (0.486–17.023)
rs11136000	11 (6.9)	0 (0.0)	28 (17.5)	2 (1.2)	9 (5.6)	7 (4.3)	0.0013	50 (15.6)	2 (0.6)	46 (14.4)	16 (4.9)	0.0182	6.521 (1.385–30.715)
−196 to −174 del	24 (15.0)	6 (3.7)	10 (6.3)	2 (1.2)	14 (8.8)	1 (0.6)	0.5102	58 (18.1)	14 (4.3)	38 (11.9)	4 (1.2)	0.256	0.436 (0.133–1.425)
rs2234693	26 (16.3)	6 (3.7)	22 (13.8)	3 (1.8)	0 (0.0)	0 (0.0)	0.716	74 (23.1)	15 (4.6)	22 (6.9)	3 (0.9)	0.75	0.672 (0.178–2.538)
rs9340799	13 (8.1)	0 (0.0)	20 (12.5)	3 (1.8)	15 (9.4)	6 (3.7)	0.0762	46 (14.4)	3 (0.9)	50 (15.6)	15 (4.6)	0.0279	4.6 (1.250–16.924)
Allele m/M	Genotype no. (%). *APOE* ε4 allele non-carriers							Allele no. (%), *APOE* ε4 allele non-carriers					OR; 95 % CI
	mm		Mm		MM		*p*	m		M		*p*	
	AD	Con	AD	Con	AD	Con		AD	Con	AD	Con		
rs1799864	1 (0.6)	20 (12.3)	3 (1.9)	57 (35.0)	108 (67.5)	77 (47.2)	<0.0001	5 (1.6)	97 (29.8)	219 (68.4)	211 (64.7)	<0.0001	0.05 (0.02–0.124)
rs333	0 (0.0)	0 (0.0)	2 (1.3)	6 (3.7)	110 (68.8)	148 (90.8)	0.473	2 (0.6)	6 (1.8)	222 (69.4)	302 (92.6)	0.477	–
rs2986017	1 (0.6)	1 (0.6)	9 (5.6)	12 (7.4)	102 (63.8)	141 (86.5)	0.9716	11 (3.4)	14 (4.3)	213 (66.6)	294 (90.2)	1	1.085 (0.483–2.436)
rs1800629	9 (5.6)	0 (0.)	54 (3.8)	16 (9.8)	49 (30.6)	138 (84.7)	<0.0001	72 (22.5)	6 (1.8)	152 (47.5)	302 (92.6)	<0.0001	23.842 (10.136–56.081)
rs1800630	0 (0.0)	1 (0.6)	9 (5.6)	4 (2.5)	103 (64.4)	149 (91.4)	0.0903	9 (2.8)	7 (2.1)	215 (67.2)	301 (92.3)	0.3651	1.8 (0.660–4.908)
rs541458	4 (2.5)	0 (0.0)	16 (10.0)	16 (9.8)	92 (57.5)	138 (84.7)	0.0366	24 (7.5)	16 (4.9)	200 (62.5)	292 (89.6)	0.0265	2.19 (1.1345–4.2273)
rs12800974	2 (1.3)	0 (0.0)	10 (6.3)	8 (4.9)	100 (62.5)	146 (89.6)	0.116	14 (4.4)	8 (2.5)	210 (65.6)	300 (92.0)	0.0617	0.4 (0.165–0.971)
rs17159904	1 (0.6)	1 (0.6)	3 (1.9)	4 (2.5)	108 (67.5)	149 (91.4)	0.9736	5 (1.6)	6 (1.8)	219 (68.4)	302 (92.6)	1	–
rs6701713	1 (0.6)	0 (0.0)	7 (4.4)	8 (4.9)	104 (65.0)	146 (89.6)	0.465	9 (2.8)	8 (2.5)	215 (67.2)	300 (92.0)	0.2899	0.527 (0.199–1.392)

Table 4 continued

Allele m/M	Genotype no. (%). *APOE* ε4 allele non-carriers							Allele no. (%), *APOE* ε4 allele non-carriers						OR; 95 % CI
	mm		Mm		MM		*p*	m		M		*p*		
	AD	Con	AD	Con	AD	Con		AD	Con	AD	Con			
rs3818361	0 (0.0)	0 (0.0)	5 (3.1)	5 (3.1)	107 (66.9)	149 (91.4)	0.746	5 (1.6)	5 (1.5)	219 (68.4)	303 (92.9)	0.749		0.723 (0.207–2.527)
rs1408077	1 (0.6)	0 (0.0)	4 (2.5)	4 (2.5)	107 (66.9)	150 (92.0)	0.45	6 (1.9)	4 (1.2	218 (68.1)	304 (93.3)	0.334		0.478 (0.133–1.714)
rs744373	10 (6.3)	0 (0.0)	16 (10.0)	13 (8.0)	86 (53.8)	141 (86.5)	0.0002	36 (11.3)	13 (4.0)	188 (58.8)	295 (90.5)	<0.001		4.345 (2.246–8.408)
rs11554585	2 (1.3)	2 (1.2)	11 (6.9)	8 (4.9)	99 (61.9)	144 (88.3)	0.327	18 (5.6)	14 (4.3)	206 (64.4)	294 (90.2)	0.6242		0.783 (0.382–1.604)
rs7561528	1 (0.6)	0 (0.0)	16 (10.0)	11 (6.7)	95 (59.4)	143 (87.7)	0.22	18 (5.6)	11 (3.4)	206 (64.4)	297 (91.1)	0.078		2.155 (1. 016–4.571)
rs11136000	31 (19.4)	26 (16.)0	65 (40.6)	119 (73.0)	16 (10.0)	9 (5.5)	0.003	127 (39.7)	171 (52.5)	97 (30.3)	137 (42.0)	0.86		1.049 (0.742–1.48)
−196 to −174 del	6 (3.8)	12 (7.4)	81 (50.6)	70 (42.9)	25 (15.6)	72 (44.2)	0.0001	93 (29.1)	94 (28.8)	131 (40.9)	214 (65.6)	0.0113		1.616 (1.128–2.316)
rs2234693	10 (6.3)	10 (6.1)	72 (45.0)	66 (40.5)	30 (18.8)	78 (47.9)	0.0005	92 (28.8)	86 (26.4)	132 (41.3)	222 (68.1)	0.002		1.799 (1.25–2.590)
rs9340799	14 (8.8)	11 (6.7)	21 (13.1)	33 (20.2)	77 (48.1)	110 (67.5)	0.32	49 (15.3)	55 (16.9)	175 (54.7)	253 (77.6)	0.29		1.288 (0.837–1.981)

AD the number of LOAD patients, *Con* controls, *CI* confidence interval, *OR* odds ratio. The significance of the *p* value was assessed at 0.003 (0.05/18 considering 18 SNPs tested)

According to our statistical results, *APOE* ε4 is a LOAD risk factor in the additive model (OR 8.430; 95 % CI 4.784–14.854), dominant model (OR 6.619; 95 % CI 3.617–12.109), and recessive model (OR 17.821; 95 % CI 4.175–76.075). In a previous study in Iran, the difference between individuals with and without a ε4 allele regarding the susceptibility to LOAD was a risk factor of 6.5 (Gozalpour et al. 2010). In the Gyungah et al. study on 7070 cases with AD and 8169 cognitively normal controls (13 cohorts), including white, African-American, and Caribbean Hispanic individuals, a APOE ε4 significant association with AD was revealed (ORs 1.80–9.05) in all groups except the Amish and Arabs (Gyungah et al. 2010). Although the contribution of *APOE* allele is known to make the strongest association with LOAD susceptibility, much remains to be learned about the contributions of loci with more modest effects identified by genome-wide association studies (GWASs).

Failing in localize additional highly penetrant LOAD susceptibility genes and regarding to pathogenic features of AD, it seems that multiple low penetrate alleles, with modest effects and related to genes with roles in calcium homeostasis, in hormonal regulation, and in the immune system, can be considered to be possible risk factors for LOAD.

CALHM1 plays a role in controlling cytosolic Ca^{2+} levels and APP processing (Marambaud et al. 2009). The P86L polymorphism minor allele in this gene was reported to be a predisposing factor in LOAD. Unlike the Japanese, the T allele distribution was increased in AD cases as compared to controls with ORs ranging from 1.29 to 1.99 in the combined population from USA, France, UK, and Italy (Dreses-Werringloer et al. 2008; Inoue et al. 2010). Although the minor allele (A) at SNP rs2986017 within *CALHM1* showed a nominally significant association with an increased risk of LOAD (nominal $p = 0.011$; OR 2.232; 95 % CI 1.223–4.073) suggesting that the A allele is the risk allele, this did not remain significant after Bonferroni correction.

Some studies propose a gender- and race-specific pattern for *ESR1*-mediated hormonal effects on clinical outcomes in LOAD (Sundermann et al. 2010; Xing et al. 2013). The recent reports demonstrate a protective effect of the x and p alleles in addition to the px haplotype of the Xbal and PvuII SNPs against LOAD in the Italian and Caucasian population (Becherini et al. 2000; Corbo et al. 2006; Lambert et al. 2001). In a case–control study involving Japanese individuals, a greater prevalence of the X and P alleles in patients versus controls was revealed. Our results present evidence that indicates the risk of dementia associated with X and P alleles and their related genotypes and haplotypes. The association was also replicated in three different genetic models, although not

all of these associations were statistically significant after adjustment for multiple comparisons (Table 3). A significant association was observed between increased risk of LOAD and X allele in participants who carried the APOE ε4 without Bonferroni correction ($p = 0.0279$), whereas the risk of LOAD regarding PP genotype and P allele was significant for participants who did not carry the APOE ε4 allele ($p = 0.002$ and $p = 0.0005$ for allelic and genotypic distribution, respectively) (Table 4).

TNFα, *CCR2*, *TLR2*, *BIN1,* and *PICALM* contribute to the LOAD pathogenesis in different ways, especially with their role in the immune system. Among different polymorphisms in the promoter of the *TNFα* gene with effects on the transcription rate and susceptibility to different diseases, rs1800629 associates with an elevated transcriptional activity. Significant elevated serum concentrations of TNFα have been reported in Alzheimer patients compared to controls (Gezen-Ak et al. 2013). In southern China, Spain, and US populations, the effect of this variant was revealed on the age of onset of LOAD (Randall et al. 2009; Alvarez et al. 2002). Similarly, the allele and genotypic distribution between case and control groups provided an evidence of the possible role of rs1800629 in LOAD pathogenesis in the Azeri Turkish population ($p < 0.001$; OR 0.12.36; 95 % CI 7.473–20.44). Allelic but not genotypic distribution in the *APOE* ε4 adjusted subgroups revealed a negative interaction between this marker and the ε4 allele of *APOE* (Table 4).

TLR2 is essential for Aβ clearance, activation of microglia, and induction of phagocytosis. *TLR2* deficiency in transgenic AD mice could increase Aβ deposition and accelerate cognitive decline (Bsibsi et al. 2002; Richard et al. 2008). Assessing the involvement of −196 to −174 Del in *TLR2* in developing LOAD suggests a significant association between this variant and the risk of LOAD in our investigation as in the Chinese population (Yu et al. 2011).

Considering adjustment for multiple comparisons, this association was confirmed in additive and dominant models. After adjustment for APOE ε4, frequency distribution of −196 to −174 Del genotypes but not alleles differed significantly between patient and control groups among non-APOE ε4 carriers (Tables 3, 4).

CCR2 is believed to mediate blood monocyte extravasation for sites of inflammation and be involved in macrophage recruitment to the injured peripheral system (Vande et al. 2003). In our study population, the occurrence of rs1799864 CCR2-64I allele polymorphism is decreased in LOAD patients ($p < 0.001$; OR 0.222, 95 % CI 0.142–0.347) and also a low frequency of the genotype 64I/64I in AD patients proved a real protective effect of this polymorphism on AD (2.5 vs 12.8 %) ($p < 0.001$). Our finding about this polymorphism is in agreement with the results of Galimberti et al. carried out on the Italian population ($p = 0.037$; OR 0.65; 95 % CI 0.41–1.03) (Galimberti et al. 2004). Our findings showed the association in dominant, recessive, and additive models. After adjustment for *APOE*, and considering Bonferroni correction, the association limited only in the group without carrying the *APOE* allele (Table 4).

BIN1 has a key role in regulating endocytosis and endolysosomal trafficking pathways that, through which APP, Aβ, and ApoE are all internalized, suggests a potential association with AD pathology (Tan et al. 2013). Higher levels of BIN1 expression have recently been reported to be associated with later age at onset and shorter disease duration in AD patients (Karch et al. 2012). In Seshadri et al. study, three-stage meta-analysis (8,371 LOAD cases and 26,965 controls) on variant rs744373 offered the strongest association with LOAD after *ApoE*, *CLU,* and *PICALM* ($p = 1.6 \times 10^{-11}$, OR 1.15) (Seshadri et al. 2010). Lambert et al. replicated the association of the *BIN1* rs744373 variant with the risk of AD in three European populations ($p = 2.9 \times 10^{-7}$; OR 1.26; 95 % CI 1.15–1.38) (Lambert et al. 2010). In our research, only *BIN1* rs744373 marker allelic association was replicated in the investigation of possible associations among three selected SNPs on BIN1 and LOAD (allelic distribution: $p < 0.0001$, OR 95 % CI 2.847 (1.562–5.187); genotypic distribution $p = 0.006$). After adjustment for *APOE* status, both allelic and genotypic distribution of this variant showed association, only among *APOE* ε4 non-carriers, with LOAD.

Significant associations between LOAD and several SNPs close to *PICALM* have been demonstrated, including rs12800974, rs17159904, and rs541458 (www.alzgene.org). Harold et al. reported the first significant evidence for these SNPs association (rs541458: $p = 8.3 \times 10^{-10}$; OR 0.86) with LOAD (Harold et al. 2009; Piaceri et al. 2011). In our study, among three variants on *PICALM*, rs541458 was associated with an increased risk for LOAD occurrence.

After adjustment for APOE status, both the allelic and genotypic association observed for this variant limited only in APOE ε4 non-carriers. This association did not remain significant after Bonferroni correction ($p = 0.0265$; $p = 0.0366$ for allelic and genotypic distribution, respectively).

Similar to other multifactorial diseases, the absence of the risk genes decreased the likelihood but does not completely rule out the disease occurrence. However, finding the LOAD associated markers in an individual raises the chances of disease from a priori risk for the general population to higher risk and increases the odds with the age of presentation. In conclusion, we have replicated *CCR2* (rs1799864), *ESRα* (*Pvu*II), *ESR*1α (*Xba*I), *TNFα*

(rs1800629) as well as *APOE,* associations with LOAD susceptibility in Azeri Turk ancestry populations in dominant, recessive, and additive models.

Our results reveal after adjusting for APOE and considering Bonferroni adjustment for multiple testing, the association with TNFα (rs1800630) (regarding allelic distribution) was evident only among subjects with the APOE ε4 allele, whereas TNFα (rs1800629) (allelic distribution), TLR2 (genotypic distribution) and CCR2, ESR1α (PvuII), and BIN1 (rs744373) (both allelic and genotypic distribution) differences between case and control groups were restricted to non-APOE ε4 carriers. It seems that the genetic effect of these variants is relevant in predisposing to LOAD only in the absence of the APOE ε4 allele, while in ε4 carriers the genetic effect is determined by this robust susceptibility factor.

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